# IMPLANTABLE POLYMER HYDROGEL FOR THERAPEUTIC USES

## TECHNICAL FIELD

(a) Field of the Invention

This invention relates to a polymer hydrogel. More particularly, the present invention is concerned with a porous, implantable polymer hydrogel for therapeutic uses, for example, which can be used for internal tissue replacement of any portion of soft organs, for wound healing, for tissue regeneration, and for organ repair in general, especially in the developing and adult nervous system, and other like therapies. The invention is especially directed at a polymer hydrogel which, upon implantation becomes a porous matrix which is filled with biological fluids and molecules to form a so-called organoid hydrogel, and becomes progressively integrated into the host by subsequent ingrowth of tissue and blood vessels. The invention also relates to a method of introducing living tissue cells, precursor cells or genetically modified cells within such polymer hydrogel to produce biohybrid materials which are useful for three-dimensional cell cultures or for tissue reconstruction. The invention also relates to a method for the production of the polymer hydrogel according to the invention, and to biohybrid materials produced by the method mentioned above. Finally, the present invention relates to a method for treating damaged parts of the central nervous system, especially the spinal cord and optic nerve, or of peripheral nerves, or other tissues by implantation therein of the polymer hydrogel or the biohydrid materials according to the invention.

## BACKGROUND ART

(b) Description of Prior Art

Organ transplantation is presently the only alternative to alleviate organ failures and to restore or improve the function and performance of organs. However, some of the drawbacks of organ-transplant therapies, are the potential for donor-to-recipients disease transmission, the shortage and the limited availability of donor organs, and possible immunological cross-reactions.

Thus, for example, spinal cord transplantation is neither clinically nor biologically feasible and consequently there is no treatment available for SCI patients, while in the United States alone there are 250,000 chronically paralyzed patients with an increase of 10,000 new SCI patients each year.

On the other hand, implantation, transplantation or injection of cells into the body to replace or restore missing cells or part of tissue organs cannot properly achieve formation of new tissues because of the lack of a supporting extracellular matrix as a necessary tissue framework for tissue expansion and organization into an integrated structure in contact with the host organ. In addition, the cells need to be placed in a physiologically-equivalent environment that facilitate diffusion of nutrients, oxygen, humoral and cellular components in order to maintain high cell viability and growth potential after implantation.

Porous hydrogels of the present invention are deformable porous polymer matrices saturated with interstitial fluid or water, and thus provide the necessary tissue framework and hydrated space through which the cells can proliferate and assemble into supracellular tissue architectures in a correct histological structure to obtain a functional neotissue.

Different experimental strategies of intraspinal transplantation have been disclosed in the literature as attempts to



restore damages in the spinal cord (animal models), using various implant materials which can be grouped into two broad categories of implants: (1) biological tissues and (2) prosthetic materials.

In category (1) is included the use of donor tissue grafts, either syngenic autograft or homograft, allograft or xenograft, to bridge lesions of spinal cord such as fetal neural tissue, either as (a) a solid graft (e.g. Bregman, Dev. Brain Res., 34, 265, 1987; Houlé and Reier, J. Comp. Neurol., 269, 535, 1988) or as (b) suspension grafts including mixed neural tissue cells (e.g. Goldberg and Bernstein, J. Neuroscience Res., 19, 34, 1988; Hoovler and Wrathall, Acta Neuropathol., 81, 303, 1991); Schwann cells recombined with cultured sensory neurons (Kuhlengel et al., J. Comp. Neurol., 293, 74, 1990); immature astrocytes (e.g., Bernstein and Goldberg, Res. Neurol. Neurosci., 2, 261, 1991); precursors of neural tissue cells (Monteros et al., Dev. Neurosci., 14, 98, 1992) and immortalized established cell lines (Zompa et al., Int. J. Dev. Neurosci., 11, 535, 1993); peripheral nerve segment including cultured non-neuronal cells (Wrathall et al, Acta Neuropathol., 57, 59, 1982) or with embryonic neural tissue (Horvat et al., Res. Neurol. Neurosci., 2, 289, 1991). For category (2) prosthetic materials which have been disclosed include pure collagen matrices (de la Torre and Goldsmith, Brain Res., Bull., 35, 418, 1994; Marchand and Woerly, Neurosci. 36, 45, 1990; Gelderg, Brain Res. 511, 80, 1990), containing neuroactive agents (Goldsmith and de la Torre, Brain Res., 589, 217, 1992) or including cultured neural grafts (Bernstein and Goldberg, Brain Res. 377, 403, 1986); treated nitrocellulose implants (Schreyer and Jones, Dev. Brain Res., 35, 291, 1987; Houlé and Johnson, Neurosci. Lett. 103, 17, 1989); collagen implants (Paino et al., J. Neurocytol., 23, 433, 1991) and polymer guidance channels of poly(acrylonitrile-vinyl chloride) (Xu et al., J. Comp. Neurol., 351, 145, 1995) enclosing Schwann cells.

These approaches focus very sharply on the promotion of axonal regeneration using various tissue substrates as sources of new axons or using complex prosthetic substrates to support and guide growing axons, and do not address the clinically relevant issue of spinal cord or brain tissue repair by regeneration of the bulk of the host tissue and remodeling of wound healing, for example, after removing necrotic or scar tissue following injury.

Polymer hydrogels have been disclosed as implants in the nervous system (Woerly et al., Biomaterials, 11, 97, 1990; Woerly et al., Biomaterials, 12, 197, 1991; Woerly et al., J. Neural Transpl. Plast. 3, 21, 1992; Woerly et al., Cell Transpl., 2, 229, 1993; Woerly et al., J. Neural Transpl. Plast., 5, 245, 1995). These hydrogels were prepared by free radical polymerization in water, using ammonium persulfate and sodium metabisulfite or persulfate and ascorbic acid as redox initiators with either hydroxyethyl methacrylate (pHEMA), glycidyl methacrylate pGMA) or N-hydroxypropyl methacrylamide (pHPMA) or a composition including the above monomers with a cross-linking agent which is either ethylene glycol and tetraethylene glycol dimethacrylate or methylene-bis-acrylamide. These gels are typically homogeneous and optically transparent with a bimodal porosity including open (accessible pore volume) and closed pores as shown by mercury porosimetry data and scanning electron microscopy; typically the porous structure for these gels is formed of parallel cylindrical capillaries of circular cross-section as shown in FIG. 1 with an average pore diameter of 7 to 13 $\mu$m. The fractional porosity is in the range of 50% to 85% for pHEMA hydrogels, 60% to 65% for pGMA hydrogels and 70% to